REPORTS ON MEDICAL RESEARCH IN CALIFORNIA*

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THE well-presented papers by Drs. Benjamin L. Freedlander and Sidney Raffel need no further comment. However, as a member of the Medical Research Committee of the California Tuberculosis Association, it is only proper to express our gratitude to the Association for the liberal support it has given these projects. When the plans for a joint financing of research work in tuberculosis was presented to the Committee on Medical Research of the National Tuberculosis Association in December, 1943, the response by members of the Committee was most enthusiastic. Some expressed the opinion that similar plans could well be formulated and executed by other local or state associations throughout the country, and comments concerning the California plans were most encouraging.

In this connection, it may not be out of place to recall that, in the judgment of experienced investigators, the accomplishments in research on tuberculosis so ably initiated and guided by Dr. William Charles White have been fundamentally of great value. A great deal has been accomplished with a relatively small investment. Everybody interested in tuberculosis and connected with the movement to suppress the infection and the disease, will read with keen satisfaction the splendid summary by Dorothy White Wilson: "Twenty Years of Medical Research," National Tuberculosis Association, 1943.

RESEARCH STUDIES CITED

Through the courtesy of the former President, Dr. Chesley Bush, the speaker became a member of the Medical Research Committee. Thus, it is only proper that a brief report on the problems which were discussed by the Medical Research Committee at the meeting in New York, December 9 and 10, 1943, should be presented.

(1) The *minimal lesion study,* from the standpoint of prognosis, type of treatment and to salvage manpower both for military and industrial needs, was considered most pressing. It is being pursued along five different avenues: (a) A study of 10,000 cases in the New York area to determine the subsequent behavior of minimal lesions characteristic of reinfection of pulmonary tuberculosis as detected in Selectees; to determine if such lesions can be classified as acceptable for military service on the basis of x-ray lesions with history and physical findings, and to assist the Surgeon General's Office in making a reasonable disposition of cases of the above type. (b) An intensive and extensive investigation of the minimal lesion as it develops among student nurses. This research is under the direction of Dr. Carroll E. Palmer of the National Institute of Health. Thus far, 38 nursing schools are participating in this study in 10 cities with approximately 3,000 nurses enrolled. It is planned to extend the study to California in the near future. (c) A third study deals with the reëxamination of the data compiled under the direction of Dr. J. D. Aronson on the value of B.C.G. vaccination of American Indians. In this research 1,000 cases vaccinated and 1,000 controls are being followed by x-ray and tuberculin tests. (d) The minimal lesions are being studied by the U. S. Army Medical Corps in cases of tuberculosis which have arisen since induction. (e) An attempt is being made to recover in the urine and serum of infected animals fractions of the tubercle bacillus to determine, if they have any prognostic value. No test of prognostic value has yet been devised.

STANDARD DRUG TEST NEEDED

(2) *Chemotherapy of Tuberculosis:* In view of the great achievement in the realm of the chemotherapy, even chemoprophylaxis of many acute infectious diseases, it is imperative that a national machinery be organized to provide and determine standard methods for testing drugs. A subcommittee, under Dr. L. U. Gardner, is engaged with the formulation of a program. In time it may be advisable to set up and financially support several centers in which the proper evaluation of promising drugs may be carried out. California should make a bid for the establishment of such a research center. To search for a cure in tuberculosis requires patience; the road is long and tortuous, full of pitfalls and disappointments. Indeed, it is doubtful if methods followed for the acute diseases are necessarily applicable to a chronic disease such as tuberculosis.

"DIASONE" PUBLICITY UNFORTUNATE

It is most unfortunate, in fact criminal, that the drug "diasone" has received nationwide publicity that it does not deserve. The chemical formula of this drug is very similar to that of "promin." In the digestive tract, both drugs break down to "diaminodiphenylsulfone," and both produce in animals haemolytic anemia with active blood regeneration. "Diasone" is slowly excreted, and consequently toxic skin reactions in form of fatal (one case) exfoliative dermatitis have been reported. Both in experimental animals and in clinical tuberculosis, "promin" has shown much greater efficacy than "diasone." According to reports, the improvements reported by Dr. Petters are not well substantiated. His criteria have not been adequate. Moreover, cavities in some patients which closed have now reopened, and other patients have developed recurrent disease while taking "diasone." Finally, definite spread of tuberculosis on patients taking full doses of "diasone" has occurred. Patients taking "promin" have not shown these complications.

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In view of these facts, it is important to emphasize again that those who have taken the Hippocratian Oath should not experiment with drugs or biologics until the research workers are in accord with regard to the principles involved, and have proved by animal tests that the preparations are effective, and produce no harm on prolonged administration. "Diasone" does not fulfill these prerequisites.

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EXPERIMENTS IN THE CHEMOTHERAPY OF TUBERCULOSIS*

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CHEMOTHERAPY in the field of tuberculosis has lagged behind chemotherapy of other bacterial infections. The reasons for this are several:

1. Tuberculosis is a more complex disease than other infections, which makes chemotherapy more difficult to evaluate. Unlike other infectious agents, the tubercle bacillus produces protean pathological lesions, depending upon allergy, environmental and genetic factors, as well as upon dosage and virulence. The infection in animals lasts many months, which makes experimentation tedious and costly.

2. No standard method or technique of evaluating new chemicals for the treatment of tuberculosis has been developed. The strain of guinea pigs, as well as the dosage and virulence of tubercle bacilli, varies with each laboratory. The type of tuberculosis seen in guinea pigs is in some ways unlike clinical tuberculosis. In guinea pigs tuberculosis is a more rapidly fatal generalized disease, without the same tendency toward periodic spontaneous regressions, or localizations of pathology as seen in patients.

Guinea pigs may react differently than patients to drugs, relative both to dosage and therapeutic effect. This was the case with promin; when treated with this drug, the guinea pig will tolerate relatively larger dosage orally, and will respond therapeutically better than patients. Theoretically, one would expect the type of tuberculosis seen in patients to respond more readily to treatment than the disseminated type of tuberculosis seen in guinea pigs.

LOW TOXICITY AN ESSENTIAL

The following are the requirements of a new therapeutic compound.

1. The chemical must be low in toxicity. It would be futile to start with compounds high in toxicity, such as the mercurials. Some twenty years ago DeWitt tested a large number of organic mercurials on tuberculosis in guinea pigs. Although they showed some therapeutic effect, they had to be abandoned because of their high toxicity.

2. The chemicals must be nonirritating.

3. They must, to a certain degree, be soluble in water or lipids.

4. They should be compatible with serum.

5. The chemicals should be bacteriostatic in vitro.

6. The compounds should finally be effective in the animal body.

The following is the sequence of testing new compounds.

1. In vitro bacteriostatic action in synthetic media (without serum).

2. In vitro bacteriostatic action in serum. As most of the new chemicals, which are effective without serum, do not show bacteriostatic action in the presence of serum, this test permits us to screen out a large number of compounds rapidly, without resorting to the costly animal procedures.

3. Toxicity in guinea pigs.

4. Therapeutic effect in guinea pigs.

5. Pharmacology of the drug.

NINETY DERIVATIVES TESTED

The author has tested some ninety derivatives of benzophenone for their tuberculostatic effect in vitro. An effort was made to determine the relation between chemical structure and bacteriostatic action. The parent compound, benzophenone, has the advantage of being low in toxicity and of showing a moderately high bacteriostatic action. The following derivatives of benzophenone increased the bacteriostatic effect :-4-chloro; 2-chloro; 2, 4'dichloro; 2-iodo; 4-methyl; 4-methoxy; 4-ethoxy; and thiobenzophenone. Among the many derivatives which decreased the bacteriostatic effect were :-3-chloro; 2, 5 dichloro; 4-ethyl; 4-hydroxy; 4-amino; and 4-nitro. It was not possible to find a definite chemical pattern in the relationship between chemical structure and tuberculostatic action. However, if the results are analyzed on the physico-chemical properties of the compounds, certain patterns were discernible, such as an optimal lipid-water solubility ratio. If guiding principles, such as the above, can be evolved, chemotherapy can proceed by more orderly and logical methods, than that of the hit-and-miss methods of the past.

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IMMUNITY PROBLEMS IN TUBERCULOSIS*

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DURING the past year we have been employing isolated constituents of the human

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